We Claim
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1. A DNA sequence which encodes an immunoglobulin superfamily (IgSF) domain or fragment which differs from a parent IgSF domain or fragment in that the region which comprised or would comprise the interface with a second domain adjoined to said parent IgSF domain or fragment within the chain of a larger IgSF fragment or protein is made more hydrophilic by modification.

2. The DNA sequence according to claim 1 in which said modification is substitution of one or more amino acids at said interface with amino acids which are more hydrophilic.

3. The DNA sequence according to claim 1 in which said modification is insertion of one or more hydrophilic amino acids in said interface, or insertion of amino acids which increase the overall hydrophilicity in said interface, or deletion of one or more hydrophobic amino acids in said interface, or deletion of amino acids, said deletion leading to an increase in the overall hydrophilicity in said interface.

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4. The DNA sequence according to claim 1 in which said modification consists of any two or more of:

a) substitution of one or more amino acids at said interface with amino acids which are more hydrophilic,

b) insertion of one or more hydrophilic amino acids in said interface, or insertion of amino acids which increase the overall hydrophilicity in said interface,

c) deletion of one or more hydrophobic amino acids in said interface, or deletion of amino acids, said deletion

leading to an increase in the overall hydrophilicity in said interface.

5. The DNA sequence according to any of claims 2 to 4 in which said substituted or inserted amino acid is taken from the list Asn, Asp, Arg, Gln, Glu, Gly, His, Lys, Ser, and Thr.

6. The DNA sequence according to any of claims 1 to 5 in which said parent IgSF domain is part of an IgSF fragment.

7. The DNA sequence according to any of claims 1 to 6 in which said domain or fragment is derived from an antibody.

8. The DNA sequence according to claim 7 in which said fragment is a Fab fragment.

9. The DNA sequence according to claim 7 in which said fragment is an Fv fragment.

10. The DNA sequence according to claim 7 in which said fragment is a scFv fragment.

11. The DNA sequence according to claim 7 in which said fragment is an Fv stabilized by an inter-domain disulphide bond.

12. The DNA sequence according to any of claims 9 to 11 in which said interface region comprises residues 9, 10, 12, 15, 39, 40, 41, 80, 81, 83, 103, 105, 106, 106A, 107, 108 for VL, and residues 9, 10, 11, 13, 14, 41, 42, 43, 84, 87, 89, 105, 108, 110, 112, 113 for VH.

13. The DNA sequence according to any of claims 1 to 12, having a contiguous sequence which encodes one or more additional moieties.

14. The DNA sequence according to claim 13 in which at least one of said additional moieties is a toxin, a cytokine, or a reporter enzyme.

15. The DNA sequence according to claim 13 in which at least one of said additional moieties is at least part of a surface protein of an organism.

16. The DNA sequence according to claim 15 in which said organism is a filamentous bacteriophage.

17. The DNA sequence according to claim 16 in which said surface protein is the geneIII protein.

18. The DNA sequence according to claim 13 in which at least one of said additional moieties is capable of binding a metal ion.

19. The DNA sequence according to claim 18 in which at least one of said additional moieties comprises at least five histidines.

20. The DNA sequence according to claim 13 in which said moiety is a peptide.

21. The DNA sequence according to claim 20 in which said peptide is a labelling tag.

22. The DNA sequence according to claim 21 in which said labelling tag is c-myc or FLAG.

23. The DNA sequence according to claim 20 in which said peptide comprises an association domain which results in self-association of two or more of said antibody fragments.

24. The DNA sequence according to claim 23 in which said association domain is derived from a leucine zipper or from a helix-turn-helix motif.

25. The DNA sequence according to claim 20 in which said peptide comprises a first association domain which results in hetero-association of one or more of said antibody fragments with one or more peptides or proteins comprising a second hetero-association domain being able to associate with said first hetero-association domain.

26. A vector comprising a DNA sequence according to any of claims 1 to 25.

27. A host cell comprising a vector according to claim 26.

28. An IgSF domain or fragment, or a fusion protein comprising an IgSF domain or fragment, encoded by a DNA sequence according to any of claims 1 to 25, by a vector according to claim 26, or produced by a host cell according to claim 27.

29. A diagnostic composition comprising an IgSF domain or fragment, or a fusion protein comprising an IgSF domain or fragment, according to claim 28.

30. A therapeutic composition comprising an IgSF domain or fragment, or a fusion protein comprising an IgSF domain or fragment, according to claim 28.

31. A method for deriving a DNA sequence according to any of claims 1 to 25 which comprises the following steps:

i) analyzing the interface region of a parent IgSF domain for hydrophobic residues which are solvent-exposed,

ii) identifying one or more of the hydrophobic residues to be substituted by more hydrophilic residues, or one or more positions where hydrophilic residues or amino acid stretches enhancing the overall hydrophilicity of the interface region can be inserted into said interface region, or one or more positions where hydrophobic residues or amino acid stretches enhancing the overall hydrophobicity of the interface region can be deleted from said interface region, or any combination of said substitutions, said insertions, and said deletions to give one or more mutants of said parent IgSF domain.

32. A method for making an IgSF domain or fragment, or a fusion protein comprising an IgSF domain or fragment, according to claim 28 which comprises the following steps:

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i) deriving a DNA sequence according to claim 31,

ii) preparing DNA encoding said mutant or mutants, said DNA being prepared either separately or as a mixture,

iii) introducing said DNA or DNA mixture in a vector system suitable for expression of said mutant or mutants, said vector system optionally comprising one or more additional DNA sequences suitable for expression of additional IgSF domains or fragments, or one or more DNA sequences suitable for expression of a fusion protein comprising said mutant or mutants, or any combination of said additional DNA sequences.

iv) introducing said vector system into suitable host cells and expressing said mutant or mixture of mutants, or expressing said mutants or mixture of mutants in combination with the expression products of said additional DNA sequences,

v) identifying and characterizing one or more mutants, alone or in said combination, which are obtained in higher yield in soluble form, and

vi) if necessary, repeating steps ii) to vi) to increase the hydrophilicity of said identified mutant or mutants, alone or in said combination, further.

33. The method according to claim 32 in which said host is a bacterium, a fungus, a plant, an insect cell, or a cell-line of mammalian origin.

34. A method for the production of an IgSF domain of fragment of claim 28 comprising culturing a host cell of claim 27 and isolating said domain or fragment.